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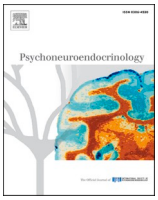

Trajectories and associations of symptoms of mental health and well-being with insulin resistance and metabolic health in women with gestational diabetes

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) is characterized by increased insulin resistance and carries perinatal and long-term risks for the mother and her offspring. There is a link between perinatal depression or anxiety and GDM. Mental health problems are associated with higher insulin resistance and could explain the underlying association between GDM and depression or anxiety symptoms. We investigated the trajectories and associations between symptoms of mental health and well-being with insulin resistance and metabolic health in women with GDM.

Methods: This study included the control group (n = 106) of a randomized controlled trial in women with GDM that were followed-up during pregnancy and up to 1-year postpartum. We measured symptoms of mental health (Edinburgh Postnatal Depression Scale (EPDS), Anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A), well-being (The World Health Organization Well-Being Index (WHO-5)) and metabolic health, including insulin resistance variables (HOMA-insulin resistance (IR) and Matsuda Index of insulin sensitivity) as well as weight during pregnancy and in the postpartum.

Results: Participants' pre pregnancy weight and BMI were 69.7 kg ± 16.1 and 25.9 kg/m^2 ± 5.5 respectively. HOMA-IR was higher during pregnancy compared to 6–8 weeks postpartum and increased between 6–8 weeks and 1-year postpartum (all $p < 0.05$). Matsuda index decreased between 6–8 weeks and 1-year postpartum ($p < 0.001$). EPDS scores decreased between pregnancy and both 6–8 weeks and 1-year postpartum (all $p < 0.05$). HADS-A scores did not change between pregnancy and the postpartum. WHO-5 scores improved significantly from pregnancy and both 6–8 weeks and 1-year postpartum ($p < 0.001$). Correlation coefficients within outcome at the three different time points were high for metabolic measures and ranged between 0.94 and 0.96 for weight, from 0.77 to 0.89 for HOMA-IR and 0.64 for the Matsuda index (all $p < 0.001$). Mental health and well-being variables were moderately correlated in all three time points including r = 0.36–0.55 for the EPDS ($p < 0.001$), r = 0.58 for HADS ($p < 0.001$), and r = 0.43–0.52 for the WHO-5 ($p < 0.01$). After adjustment for age and pre-pregnancy BMI, Matsuda index was negatively associated with EPDS scores and positively associated to WHO-5 scores at 6–8 weeks postpartum. No other association between insulin resistance and mental health or well-being outcomes were found.

Conclusion: While insulin resistance fluctuated with values being lowest in the early postpartum and increasing thereafter, both depression and well-being scores decreased between pregnancy and the postpartum and did not change in the postpartum period. Intraindividual variability was larger for mental health and well-being than for metabolic health outcomes at different time points, indicating a higher plasticity for mental health and well-being outcomes that could be acted upon. We found only few associations between mental health and well-being and metabolic health outcomes.

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1. Introduction

Approximately 15% of pregnant women are affected by GDM globally with variations between regions, ethnicity, and diagnostic thresholds (Guariguata et al., 2014). In Europe, the prevalence of GDM is around 11%, with the highest prevalence in Eastern European countries (31.5%) (Paulo et al., 2021). The prevalence of GDM in Switzerland is estimated to be 10.8%, between 2010 and 2012, according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) guidelines for screening and diagnosis of GDM (Ryser Rüetschi et al., 2016). GDM is associated with adverse neonatal and obstetric outcomes including gestational hypertension and preeclampsia (Pérez-Pérez et al., 2020), preterm deliveries, and low birth weight (Gilbert et al., 2019). The association between mental health issues and GDM has been the subject of several studies with identification of a complex and bidirectional relationship (Riggin, 2020; OuYang et al., 2021). It has been reported that in women with GDM, the prevalence of anxiety symptoms varies between 33% and 59% during pregnancy (Faisal-Cury and Rossi Menezes, 2007) and from 11% to 20% during postpartum (Brassel et al., 2020). Women with GDM have a 2–4 fold increased risk of symptoms of depression during the perinatal period compared to women without GDM (Hinkle et al., 2016). One third of women with GDM experience postpartum depression (Gilbert et al., 2019) and higher depression scores in the early pregnancy predict later GDM (Hinkle et al., 2016). On the other hand, anxiety and/or depression in early pregnancy increase the risk of future GDM (OuYang et al., 2021). Independent of GDM, maternal mental health issues have been associated with the risk of poor maternal and offspring outcomes, such as retained maternal weight postpartum (Wikman et al., 2020) increased risks of preeclampsia, preterm births and fetal growth impairment (Howard and Khalifeh, 2020).

Inflammation and oxidative stress (Renugasundari et al., 2023), the activation of the hypothalamic–pituitary–adrenal (HPA) axis (Riggin, 2020) and changes in sex steroids hormones (Clark et al., 2019) are potential factors explaining the association between depression and GDM. Shared environmental risk factors and the burden of GDM management could also explain the association between those two conditions. Symptoms of depression can lead to unhealthy behaviors, such as physical inactivity, and increased caloric intake (Bowers et al., 2013; Morrison et al., 2016) all of which influence GDM. Furthermore, transition to become a mother is a stressful transition involving processes to reorganize inner thoughts and external behaviors (Pan et al., 2019). This is a crucial period for redefining identity, physical image, maternal attachment and confidence regarding the maternal role (Hwang et al., 2022). Becoming a mother is a transformative event both at a physiological and psychological level, including hormonal fluctuations and changes in maternal brain structure (Servin-Barthet et al., 2023). This transition might be even more difficult with additional stress associated with the diagnosis of GDM, as seen in type 1 diabetes (Rasmussen et al., 2013). Outside of pregnancy, a potential link between insulin resistance itself and worsened mental health outcomes has been evoked and particularly among type 2 diabetes (Fernandes et al., 2022; Lyra Silva et al., 2019). Insulin seems to have functions in neurotransmitters regulation, including modulation of dopamine and serotonin reuptake and enzymatic degradation (Kleinridders and Pothos, 2019; Leonard and Wegener, 2020). Insulin receptors are expressed in cerebral regions involved in mood regulation (Hamer et al., 2019) modulates feeding behavior and energy maintenance by the hypothalamus (Lyra Silva et al., 2019; Mansur et al., 2018). By taking those physiopathological elements into consideration, insulin resistance can cause hyperphagia, anxiety and depressive-like behavior (Kleinridders and Pothos, 2019).

To our knowledge, only one study has investigated the association between insulin resistance and mental health in the general pregnant women, but not in the GDM population. In that study, maternal stress was associated with increased insulin resistance during pregnancy (Valsamakis et al., 2017). Furthermore, studies based on the trajectory of mental health during the perinatal period among healthy women identified distinct pathways and significant heterogeneity regarding onset and the severity of the trajectories were found across the different studies (Wikman et al., 2020).

In the context of the high prevalence of perinatal mental health problems and GDM and their adverse consequences, the aim of this study was to assess the trajectories and intraindividual variability of different mental health, well-being, and metabolic health outcomes, during pregnancy and the postpartum in women with GDM. We also determined whether their mental health was associated with metabolic health at different time points.

2. Method

2.1. Study design

This study is a secondary analysis of the MySweetheart trial. This randomized controlled intervention trial (MySweetHeart trial; NCT02890693) included 211 women with GDM that were followed up during pregnancy and up to 1-year postpartum. Details of the study protocol are already described elsewhere (Horsch et al., 2018). Briefly, the intervention consisted of a multidimensional interdisciplinary lifestyle and psychosocial intervention, which was compared with a guidelines-based treatment as usual care control group. The allocation ratio was 1:1 using a block randomization method (blocks of 4) after stratification. The Human Research Ethics Committee of the Canton de Vaud approved the study protocol ((2016–00745)).

2.2. Participants

Women diagnosed with GDM according to IADPSG criteria at 24–32 weeks of gestational age were included (Blumer et al., 2013). Women with GDM $\geq$ 18 years who understood French or English and consented to participate were eligible for inclusion. Women on strict bed rest, with severe mental health disorder and pre-existing diabetes were excluded from the study. Severe mental health disorders included the presence of current psychotic episode or acute suicidal risk (Horsch et al., 2018). Strict bed rest was an exclusion criterion because these women were not able to attend in-person study visits. For the present analysis, we only included women allocated to the control group (n = 106). Women in the intervention group were not included because of the potential impact of the intervention (physical activity, etc.) on insulin resistance and mental health.

2.3. GDM diagnosis and follow-up

Participants in the control group received treatment-as-usual GDM care based on the American Diabetes Association and on the Endocrine Society guidelines (American Diabetes Association, 2023; Blumer et al., 2013). Women had regular appointments every 1–3 weeks with a medical doctor, a diabetes-specialist nurse and/or a dietician after the GDM diagnosis. In our current practice, women diagnosed with GDM by private practices are referred to our university hospital for the first GDM visit; this usually takes 1–3 weeks depending on the availabilities of the patients and the clinical. During the first visit, women received information on GDM and were taught how to perform self-monitoring of blood glucose control four times during the day.

2.4. Measures

They were also advised on gestational weight gain based on the Institute of Medicine (IOM) 2009 recommendations and on dietary modifications (Rasmussen et al., 2009; Sox and Greenfield, 2009). Patients had one dietary counseling appointment with a registered dietician that focused on distributing carbohydrate intake over several meals and snacks, limiting the intake of free sugars to less than 10% and

increasing fiber intake to up to 30 g per day. Free sugars included both added and natural sugars present in sweetened products such as desserts, fruit juices, honey, and high-fructose corn syrup or sugar-sweetened beverages (Debras et al., 2020; Mussa et al., 2021). Women were encouraged to increase physical activity according to the Endocrine Society Guidelines (Blumer et al., 2013). If glucose values remained above targets between two or more times during a 1–2-week period (fasting glucose > 5.3 mmol/l, 1-h postprandial glucose >8 mmol/l and/or 2-h postprandial glucose >7 mmol/l) despite lifestyle changes, metformin or insulin treatment was introduced depending on patients glucose values and preference and according to guidelines (Arditi et al., 2018). The 6–8 weeks and 1-year postpartum follow-up visits included an assessment of the overall and metabolic situation and counseling on lifestyle changes based on cardio-metabolic laboratory and anthropometric results including screening for type 2 diabetes in women at 6–8 weeks postpartum, using the 75-g oral OGTT (ACOG Practice Bulletin No. 190, 2018; American Diabetes Association, 2023).

Outcomes were evaluated at their first GDM visit in the second trimester in pregnancy, at 6–8 weeks and at 1-year postpartum. Mental health outcomes included depression and anxiety symptoms, well-being and metabolic outcomes included weight and insulin resistance with a focus on the latter.

2.4.1. Mental health outcomes

The Edinburgh Postnatal Depression Scale (EPDS) was used to evaluate maternal symptoms of depression during pregnancy and in the postpartum. This 10-item questionnaire is one of the most widely used scales in the perinatal period, including the postpartum period and has good psychometric properties (Shrestha et al., 2016; Sultan et al., 2022b). The EPDS has been validated in French (Guedeney and Fermanian, 1998). Each item is scored on a 4-point scale and the total score ranges from 0 to 30 points, with a higher score indicating more severe symptoms of depression (Cox et al., 1987) and reflects symptoms of depression for the 7 preceding days. Cut-off of 12.5 has been suggested originally as an indicator of clinically significant depression (Cox et al., 1987) but some authors reported a cut-off score of 10 in a French sample of postnatal women (Guedeney and Fermanian, 1998).

We measured anxiety symptoms with the Anxiety subscale of the Hospital Anxiety and Depression (HADS) at the first GDM visit and at 1-year post-partum. It has been shown to have validity and consistency in measuring anxiety and depression (Smarr and Keefer, 2011). This questionnaire focuses on affective symptoms and avoids somatic symptoms that could be induced by pregnancy itself (Lee et al., 2007). To avoid redundancy with the EPDS, only the Anxiety Subscale was used for the current analyses and consists of 7 items, each one is scored from 0 to 3 with a total score ranging from 0 to 21 and higher scores indicating greater anxiety (Zigmond and Snaith, 1983). To simplify the terminology, we used the term HADS-A referring to this Anxiety Subscale. Scores from 8 to 10 indicate possible clinical disorder and scores between 11 and 21 indicate probable clinical disorder (Bjelland et al., 2002; Feinstein et al., 1999). Furthermore, it may be used as a measure of symptom severity from normal (0−7), mild (8−10), moderate (11−14), to severe (15−21) (Pais-Ribeiro et al., 2018). This tool has been translated and validated in many countries, including in a French-speaking population and has good psychometric properties (Bocéréan and Dupret, 2014).

2.4.2. Maternal well-being

Maternal well-being was assessed with the World Health Organization Well-Being Index (WHO-5) (Topp et al., 2015). This 5-item self-report questionnaire has excellent internal consistency (Lara-Cabrera et al., 2020). It has adequate validity, both as a screening tool for depression and as an outcome measure in clinical trials, and has been applied successfully across a wide range of study fields (Hochberg et al., 2012). Items are measured on a 5-point Likert scale ranging from 0 'at no time' to 5 'all of the time', assessing the subjective well-being of the respondents. The total score from the 5-item is then multiplied by 4 to obtain the final score. Possible scores range from 0 to 100, with higher scores reflecting higher well-being status. The WHO-5 questionnaire showed satisfactory psychometric properties in a large sample of French diabetic patients (Hochberg et al., 2012). The scale has been used extensively in endocrinology research (Topp et al., 2015).

2.4.3. Sociodemographic and anthropometric variables

We collected information on maternal socio-demographic characteristics during a structured face-to-face interview at the first GDM clinic visit. This included age, nationality/ethnic origin (Switzerland, Europe or North America, Africa, Asia, Latin America, and others), educational level (compulsory school achieved, general and vocational training levels, high school, and university) and employment status (student, employed, unemployed, at home/homemaker). Information on previous history of GDM (yes/no), family history of diabetes (yes/no), history of psychiatric diagnosis (yes/no), gravida (one, two and ≥ three), parity (none, one, two and ≥ three), social support during pregnancy (yes/no) and habits (smoking status and alcohol intake during pregnancy) were taken from participant's medical charts. Need for glucose-lowering medical treatment (insulin, very rarely metformin or none), the type of deliveries and breastfeeding at 6–8 weeks postpartum (yes/no) were also extracted from the charts. Data on the use of contraception was not recorded in our study.

2.4.4. Metabolic measures

Pre-pregnancy weight was extracted from participants' medical charts or, very rarely, if missing, was self-reported. We measured height and weight at the first and last GDM visit and at 6–8 weeks postpartum to the nearest 0.1 cm and 0.1 kg, respectively, with regularly calibrated electronic scales (Seca®). BMI was expressed as a ratio of weight in kilograms to the square of height in meters (kg/m^2).

2.4.5. Insulin resistance/sensitivity indices

To measure indices of insulin resistance/sensitivity, we measured glucose and insulin values every 30 min over a 2 h period during the oral glucose tolerance test (OGTT) at 6–8 weeks and 1-year postpartum. Whole body insulin sensitivity was estimated with the Matsuda index using glucose and insulin concentrations measured every 30 min over 120 min (Matsuda and DeFronzo, 1999). Matsuda index is measure of insulin sensitivity, so lower values indicate higher insulin resistance. It was not calculated during the first GDM visit to avoid a second OGTT test, few weeks after GDM diagnosis in order to decrease the burden for the participants.

The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was used as a simple measure of insulin resistance. This was calculated as the product of fasting plasma glucose (FPG) and insulin divided by a constant, 22.5 (Simental-Mendía et al., 2020).

$$\mathrm{HOMA-IR} = \frac{\mathrm{Go(mmol/l)} \times \mathrm{Io(\mu U/ml)}}{22.5}$$

2.5. Statistical analysis

All analyses were performed with Stata/SE 15.0 (StataCorp LLC, TX, USA). All descriptive variables were expressed as means (± standard deviations) or in percentages (%). All the outcome variables (EPDS, WHO-5, HADS-A, HOMA-IR and Matsuda index) were normally distributed. To assess the trajectories of the outcomes (EPDS, HADS-A, WHO-5, HOMA-IR, Matsuda index and weight/BMI) across the perinatal period, we used a repeated measures ANOVA with additional Bonferroni correction to determine if the differences of each outcome between the different time points (between first GDM visit and 6–8 weeks postpartum, first GDM visit and 1-year postpartum and between 6 and 8 weeks to 1-year postpartum) were statistically different (Table 3).

To assess the intraindividual variability of measures, we also

calculated correlations within mental health and well-being variables (EPDS, HADS-A, WHO-5) across the different time points (first GDM visit and 6–8 weeks postpartum, first GDM visit and 1-year postpartum, 6–8 weeks postpartum and 1-year postpartum) and the correlations within metabolic health indices (HOMA-IR, Matsuda index, weight, and BMI).

Multiple linear regression analyses were performed to determine the cross-sectional associations between mental health and well-being (EPDS, HADS-A, WHO-5 as the predictors) and indices of insulin resistance (HOMA-IR, Matsuda index) during pregnancy as well as in the postpartum (Table 3). In the first regression model (Model 1), we did not adjust for any cofounding variable. In model 2, we adjusted for gestational age, maternal age and pre-pregnancy BMI when the outcome variable was at the first GDM visit. When no outcome at first visit was included, we only adjusted for maternal age and BMI at respective time points. All statistical significances were two sided and accepted at $p < 0.05$.

3. Results

3.1. Samples characteristics

Table 1 shows demographic and health characteristics of participants. The mean age of participants was 33 ± 5 years, the mean gestational age was 27 ± 3 weeks, and the mean pre pregnancy BMI was 26 ± 6 kg/m^2. About 10% of the participants had a previous history of GDM and 44% needed glucose-lowering medical treatment during pregnancy. Fifteen women (14%) reported having a history of a psychiatric disorder. 31% of women had caesarian section and 63% had vaginal deliveries, while data were missing for 6% of women (mostly due to delivery in other hospitals). At 6–8 weeks postpartum, a large majority of women were breastfeeding and at 1-year postpartum, only few were breastfeeding. At 6–8 weeks postpartum, 53 women (51%) were breastfeeding exclusively, 27 (26%) had mixed breastfeeding (formula and breastfeeding) and 14 women had started breastfeeding but stopped before the 6–8 weeks postpartum visit. A minority of the participating women (2 women) used bottle-feeding with formula. At 1-year postpartum, the rate of exclusive breastfeeding was only 3%. 16% of the mothers had mixed breastfeeding (see Table 2).

3.2. Trajectories and intraindividual variability of mental health symptoms, well-being, and insulin resistance

Table 3 shows the trajectories of weight, BMI, and insulin resistance indices, as well as mental health symptoms and well-being over the three time points (first GDM visit, 6–8 weeks and 1-year postpartum). There was an overall change over time for all outcomes, except for the HADS-A. Mean weight and BMI decreased between first GDM visit and 1-year postpartum. HOMA-IR was significantly higher during pregnancy compared to 6–8 weeks postpartum and increased between 6–8 weeks and 1-year postpartum, ($p < 0.001$). The Matsuda index decreased between 6–8 weeks and 1-year postpartum, indicating an increase in overall insulin resistance during the postpartum period ($p < 0.001$). EPDS scores changed over time ($p < 0.001$). Scores decreased from the first GDM visit to both 6–8 weeks and 1-year postpartum (both $p < 0.05$). The HADS-A did not change between pregnancy and the postpartum. The WHO-5 scores improved over time ($p < 0.001$) by increasing from the first GDM visit to both 6–8 weeks and 1-year postpartum ($p < 0.05$).

There was a moderate correlation of mental health and well-being outcomes between all three time points with a correlation coefficient between 0.36 and 0.55 for the EPDS scores (all $p \leq 0.001$), 0.58 for the HADS-A scores ($p < 0.001$) and between 0.43 and 0.52 for the WHO-5 scores (all $p \leq 0.01$).

We found a high correlation between metabolic health outcomes between all three study time points. This was particularly pronounced for weight. Thus, the correlation coefficient ranged between 0.94 and 0.96 for weight, 0.77–0.89 for HOMA-IR and was 0.64 for the Matsuda index (all $p < 0.001$; see details in Supplementary Table 1).

Table 1
Demographic and health characteristics of study participants.

	All (N = 106)[a]		
	Mean ± SD	Frequency	Percent (%)
Age (years)	32.8 ± 4.7		
GA[b] at GDM[c] diagnosis (weeks)	26.9 ± 3		
GA at the first GDM visit (weeks)	29.1 ± 2.5		
Pre pregnancy weight (kg)	69.7 ± 16.1		
Pre pregnancy BMI kg/m^2 (n = 105)	25.9 ± 5.5		
Nationality/ethnic origin (n = 98)			
Switzerland		30	30.6
Europe/North America		44	44.9
Asia/Western pacific		7	7.1
Africa		14	14.3
Latin America		2	2.0
Others		1	1.0
Previous history of GDM[d]			
Yes		11	10.4
Family history of diabetes			
Yes[e]		73	68.9
History of psychiatric diagnosis			
Yes		15	14.2
Social support			
Yes		92	86.8
Educational level (n = 94)			
Compulsory school achieved		11	11.7
CFC[f]		23	24.5
High school		10	10.6
University		50	53.2
Employment status (n = 94)			
Student		5	5.3
Employed		71	75.5
Unemployed		9	9.6
At home/housewife		9	9.6
Gravida			
1		46	43.4
2		25	23.6
≥ 3		35	33
Parity			
0		63	59.4
1		26	24.5
2		9	8.5
≥ 3		8	7.5
Smoking status during pregnancy			
Yes		15	14.2
Alcohol intake during pregnancy			
Yes		8	7.5
Need for glucose-lowering medical treatment			
None		59	55.7
Insulin		45	42.45
Metformin		2	1.9
Caesarian deliveries		33	31

All results are frequency and percentage unless otherwise stated
Legend for Table 1
[a] n = 106 unless note otherwise
[b] GA means gestational age
[c] GDM means gestational diabetes mellitus
[d] only investigating women with a parity of ≥ 1
[e] yes denotes first degree relationship of the participant (e.g., mother, father, brother, and sister) or those with second-degree relationship with the participant (e.g., grandchildren, grandparent, nephew, niece, half-sister, or half-brother)
[f] CFC means general and vocational education

3.3. Associations between mental health symptoms and well-being and insulin resistance during pregnancy

Table 4 shows the cross-sectional associations between insulin

Table 2
frequency and percent of participants with breastfeeding during postpartum.

Breastfeeding	6–8 weeks postpartum		1-year postpartum	
	Frequency	Percent	Frequency	Percent
Exclusive breastfeeding	53	51%	2	3%
Mixed breastfeeding	27	26%	10	16%
Stopped	14	14%	37	58%
No	2	2%	2	3%

Table 3
Changes in mental health outcomes and well-being and indices of insulin resistance in pregnancy and in the postpartum.

	First GDM visit	6–8 weeks post-partum	1-year postpartum	Overall p-value
Weight (kg)	80.3 ± 15.9[a,b]	74.5 ± 16.4[a]	72.7 ± 17.4[b]	< 0.001
BMI (kg/m^2)	29.8 ± 5.2[a,b]	27.7 ± 5.5[a]	27.1 ± 5.9[b]	< 0.001
HOMA-IR[1]	3.6 ± 2.2[a]	2.2 ± 2[a,c]	3.3 ± 2.5[c]	< 0.001
Matsuda index[2]	N/A[7]	7.02 ± 3.4[c]	4.8 ± 2.7[c]	< 0.001
WHO-5[3]	56.5 ± 17.6[a,b]	63.4 ± 16.6[a]	65.4 ± 15.8[b]	< 0.001
EPDS[4]	7.5 ± 4.7[a,b]	6 ± 4.2[a]	5.9 ± 3.6[b]	< 0.001
HADS-A[5]	± 3.8	N/A	5.94 ± 3	0.510

Analyses were done using repeated measures ANOVA with Bonferroni correction
[1]HOMA-IR denotes Homeostatic Model Assessment for Insulin Resistance
[2]Matsuda denotes Matsuda Index
[3]WHO-5 denotes The World Health Organization Well-Being Index
[4]EPDS denotes Edinburg Postnatal Depression Score
[5]HADS-A denotes the anxiety subscale of the Hospital Anxiety and Depression Scale
[6]N/A denotes not applicable (outcome was not measured at this time point)
[a] $p < 0.05$ for differences between first GDM visit and 6–8 weeks post-partum
[b] $p < 0.05$ for differences between first GDM visit and 1-year post-partum
[c] $p < 0.05$ for differences between 6 and 8 weeks and 1-year post-partum

resistance and mental health symptoms and well-being during pregnancy and postpartum. We found no significant association between insulin resistance and mental health or well-being in the unadjusted analyses. After adjusting for age and pre-pregnancy BMI, Matsuda index was inversely associated with the EPDS depression scores (β coefficient = −0.19, p value = 0.03) and was positively associated with the WHO-5 scores (β coefficient = 0.06, p value = 0.005), both at 6–8 weeks postpartum. We found similar results when insulin resistance/sensitivity indices were the predictors and the mental health outcomes the dependent variables (Supplementary Table 2) independent of age and pre-pregnancy BMI.

4. Discussion

In our longitudinal study of women with GDM, we observed an overall change over time for metabolic indices and mental health symptoms and well-being, except for the HADS-A scores. Insulin resistance decreased between pregnancy and 6–8 weeks postpartum and then increased again up to 1-year postpartum. Depression symptoms and well-being scores improved between pregnancy and the early postpartum period and were then stable up to 1-year postpartum. Weight and insulin resistance indices correlated strongly to each other over all the three time points, whereas mental health and well-being indices correlated moderately to each other over all the three time points, indicating a higher intraindividual variability over time for mental health and well-being outcomes. Despite a higher prevalence of depression in women with GDM compared to women with healthy pregnancies (Delanerolle et al., 2021), we found associations between Matsuda index of insulin sensitivity with mental health symptoms, in the early postpartum in the adjusted analyses, but not between other mental and metabolic health outcomes.

Understanding the trajectories and relationship between GDM, metabolic and mental health and well-being could provide additional strategies for clinical management of this population. To our knowledge, this study is the first to compare the trajectories and the associations

Table 4
Cross-sectional correlations between mental health outcomes and well-being (independent variables) and indices of insulin resistance (dependent variables) during pregnancy and in the postpartum.

	HOMA-IR[a]				Matsuda[b]			
	Model 1[c]		Model 2[d]		Model 1		Model 2	
	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value
During the first GDM visit								
WHO-5[e]	-0.01 (−0.04 to 0.14)	0.33	-0.02 (−0.04 to 0.01)	0.16	N/A[h]		N/A	
EPDS[f]	0.60 (−0.05 to 0.16)	0.27	0.05 (0.04–0.13)	0.28	N/A		N/A	
HADS-A[g]	-0.04 (−0.24 to 0.17)	0.73	-0.03 (−0.23 to 0.17)	0.75	N/A		N/A	
At the 6–8 weeks postpartum								
WHO-5 Index[e]	0.003 (−0.02 to 0.03)	0.82	-0.01 (−0.01 to 0.33)	0.37	0.38	0.15	0.06** (0.02–0.10)	0.005
EPDS[f]	0.0001 (−0.1 to 0.10)	0.995	0.39 (−0.48 to 0.13)	0.38	-0.09	0.37	-0.19* (−0.35 to 0.24)	0.030
At 1-year postpartum								
WHO-5[e]	0.004 (−0.03 to 0.04)	0.81	-0.01 (−0.31 to 0.12)	0.63	0.01	0.70	0.001 (−0.03 to 0.03)	0.97
EPDS[f]	-0.01(−0.16 to 0.14)	0.88	0.01 (−0.1 to 0.12)	0.24	0.05	0.62	0.04 (−0.1 to 0.18)	0.56
HADS-A[g]	-0.11 (−0.29 to 0.07)	0.22	-0.08 (−0.2 to 0.05)	0.21	0.01	0.97	0.05 (−0.11 to 0.21)	0.58

The outcomes of insulin resistance (dependent variables) are shown at the same time points as the mental health predictors (independent variables).
*$p < 0.05$
* *$p < 0.01$
* **$p < 0.001$
[a] HOMA-IR denotes Homeostatic Model Assessment for Insulin Resistance
[b] Matsuda denotes Matsuda Index
[c] Model 1: Unadjusted linear regression estimates.
[d] Model 2: Linear regression analyses adjusted for GA at the first GDM visit, maternal age, pre-pregnancy BMI for the first GDM visit. For the postpartum visits, we only adjusted for maternal age and pre-pregnancy BMI
[e] WHO-5 denotes The World Health Organization Well-Being Index
[f] EPDS Depression Score denotes Edinburg Postnatal Depression Score
[g] HADS-A Anxiety denotes the anxiety subscale of the Hospital Anxiety and Depression Scale
[h] N/A denotes not applicable (outcome was not measured at this time point)

between insulin resistance and mental health symptoms, as well as well-being across the perinatal period in a more high-risk women with GDM.

The trajectory of insulin resistance across healthy pregnancy has been well established. Insulin resistance increases from pregnancy to early pregnancy to reach the maximum at 36 weeks of gestational age and falls after delivery (Buchanan and Xiang, 2005; Lacroix et al., 2013). The level of insulin resistance in late pregnancy is comparable to patients with impaired glucose tolerance or newly diagnosed with type 2 diabetes (Lacroix et al., 2013). Among women with GDM, there is an imbalance between higher insulin resistance and reduced capacity of pancreatic β-cells to respond to this increase in insulin resistance (Lacroix et al., 2013). In accordance with the literature, insulin resistance improved between the end of pregnancy and the early postpartum in our longitudinal study of women with GDM (Lacroix et al., 2013). In addition, we observed a second phase characterized by increased insulin resistance from early postpartum to 1-year postpartum (increase of HOMA-IR by 40%) in our study. This is coherent with the longer-term inherent risk of developing metabolic syndrome and type 2 diabetes after GDM. In fact, women with history of GDM have a 25% incidence of metabolic syndrome within 5 years postpartum, 70% of developing type 2 diabetes and 2–3 increased risk of cardiovascular diseases in the 10 years postpartum (Thayer et al., 2020), the latter even in the absence of diabetes (Kramer et al., 2019; Gunderson et al., 2021). The increase in insulin resistance between early and late postpartum could also be explained by the decrease in breastfeeding rate at 1-year postpartum. According to Retnakaran et al. (2010), GDM women show a decrease in the insulin sensitivity index from 3 months postpartum to 1-year postpartum, similarly to what we found (Retnakaran et al., 2010).

The trajectories of symptoms of depression and maternal well-being improved between pregnancy and the early postpartum and remained stable between the early and late postpartum among women with GDM. A study that showed a slight decrease in mild depression symptoms between the second trimester of pregnancy and up to 18 months postpartum among healthy women is consistent with our results (Pellowski et al., 2019). In a longitudinal study among low-risk women, 21% presented symptoms of depression from 8 months pregnancy to 2 years postpartum, with a higher intensity during pregnancy (Sutter-Dallay et al., 2012). In a large population-based cohort-study in Sweden, five trajectories of symptoms of depression were reported (Wikman et al., 2020). Healthy pregnancy (defined by EDPS score < 13 during pregnancy and < 12 during the postpartum) represented the majority of the cohort (60.6%) (Wikman et al., 2020). 8.5% reported symptoms of depression during the second trimester of pregnancy, 10.9% were diagnosed with early postpartum onset (6 weeks postpartum) of symptoms of depression and 5.4% during late postpartum (6 months) (Wikman et al., 2020). 14.6% reported chronic symptoms of depression (Wikman et al., 2020). Despite some clear distinct pathways identified in studies investigating perinatal trajectories of symptoms of depression among healthy women and the agreement that symptoms of depression are not static and show a changing course (Lee et al., 2007), heterogeneity between studies is high. Our results could be explained by the fact that these women were continuously followed by the clinical diabetes team once diagnosed with GDM and that could explain the improvement of symptoms of depression and well-being between pregnancy and the postpartum. This is furthermore supported by the relatively low mean depression scores in the postpartum.

For postpartum depression, women with GDM are at an increased risk of developing postpartum symptoms of depression (Arafa and Dong, 2019). A population-based birth cohort reported trajectories of symptoms of depression during the postpartum period up to 36 months, among healthy women and GDM women constituting 10% of the cohort (Putnick et al., 2020). In this study, different pathways were identified with the majority of women presenting low-stable symptoms of depression at all time points (Putnick et al., 2020). 8.2% of the cohort presented low symptoms of depression at the beginning of the study followed by an increase from 12 months postpartum to 36 months. Evolvement of symptoms of depression during the perinatal period could also be explained by the changing nature of symptoms across the perinatal period (Phua et al., 2020). It has been shown that during pregnancy, women report "Feeling worthless, disturbing thoughts or agonizing over past failures" (page 8) (Phua et al., 2020), whereas in the postpartum they report "feeling overwhelmed and with excessive worries" (page 9) (Phua et al., 2020). However, precise trajectories of depressive symptoms experienced by women with GDM from pregnancy to the postpartum period show inconsistent results in the literature. According to a prospective Chinese longitudinal study, the prevalence rates of depression during the first, second, and third trimesters, as well as the postpartum period, were recorded at 17.2%, 6.9%, 6.8%, and 9.0%, respectively (Li et al., 2022). Interestingly, GDM did not correlate with any trajectory of depression (Li et al., 2022). In a cohort study of 341 GDM women, mental health improved significantly between the third trimester of pregnancy and the postpartum period (6–8 weeks postpartum) (Gilbert et al., 2021).

Trajectories of well-being across the perinatal period have been studied to a lesser extent in the existing literature. In a previous cohort study of 341 GDM women performed in our center, mental health improved significantly between the third trimester of pregnancy and the postpartum period (6–8 weeks) (Gilbert et al., 2021).

Anxiety symptoms did not change across the perinatal period in our cohort. A prospective cohort study showed a mean decrease in anxiety symptoms from pregnancy (18th and 32th week) to postpartum (8th week and 8 months) among healthy pregnant women (Heron et al., 2004). In an Australian cohort, women with GDM had a higher level of anxiety at the time of the first assessment, during GDM diagnosis, compared with healthy pregnant women but there were no group differences before delivery and in the postpartum period (Daniells et al., 2003). This study underlines the potential impact of GDM diagnosis on pregnant women and the possibilities for medical health care to explore mental health and provide individualized interventions to decrease maternal anxiety during this high-risk period. In our study, anxiety was comparable between pregnancy (filled out around 1–3 weeks after GDM diagnosis) and 1 year postpartum.

The strength of the correlations within each outcome in the perinatal period from the third trimester of pregnancy to 1-year postpartum was strong for metabolic health variables, particularly weight. It was only moderate for depression and anxiety symptoms and well-being, indicating that metabolic outcomes were stable and less modulable across perinatal period and that mental health and well-being have a higher intraindividual variability and are thus more susceptible to external influences. This is surprising, as the clinical care during pregnancy and in the postpartum in these women focuses a lot on weight and weight gain or changes. One could hypothesize that it is more difficult to make very pronounced weight changes in this perinatal period or that our approaches for this would need to be revised. On the other hand, the larger variability of changes in depression scores and wellbeing gives room for interventions during this time period.

The present study did not find significant associations between mental health and metabolic health outcomes in most analyses. Thus, we only found moderate correlations between lower maternal depression and higher well-being scores and lower insulin resistance at 6–8 weeks postpartum in both directions, when data were adjusted for age and BMI. A previous study showed significant associations between maternal stress/anxiety symptoms and lower insulin sensitivity and inverse correlation between maternal stress/anxiety symptoms and insulin sensitivity; these results are inconsistent with ours (Valsamakis et al., 2017). It has been hypothesized that catecholamines secretion and activation of the sympathetic system may explain the positive association found in their study (Valsamakis et al., 2017). Reasons for differences between both studies could be linked to the fact that we investigated women with GDM and not healthy pregnancies and that our women had a clinical follow-up which may have impacted on the mental or metabolic health outcomes. Although the literature shows bidirectional associations

between the diagnosis of GDM and mental health, the temporality of these conditions remains unknown (Riggin, 2020).

4.1. Strengths and limitations

This study has many strengths, including the prospective design with longitudinal follow-up up to 1-year postpartum, the use of validated indices to measure insulin resistance including an estimation of the whole-body insulin sensitivity (the Matsuda index). We also used validated tools that has been widely used to measure mental health. Nevertheless, some limitations need to be reported. First, the size of our sampling was relatively small. Secondly, it would have been interesting to complete our questionnaires with clinical interviewers to provide accurate details on the nature of symptoms of depression and anxiety. Although we presented descriptive data on breastfeeding, we did not adjust for it in our regression models and this represents a limitation of the study considering the impact of breastfeeding in women after GDM and its association with maternal mental health, also as the exact duration of breastfeeding was not known for most women (Pezley et al., 2022). Further potential limitations are that we did not include other cofounders such as social support, the use of psychotropic drugs during pregnancy, or their financial situation of the family, as the latter is hardly asked in studies in the cultural setting of Switzerland due to ethical considerations. We did not adjust for insulin or metformin, as they were added after the first visit and stopped at delivery and thus should not impact on our data during pregnancy or at 6–8 weeks postpartum. Furthermore, only 2 women were treated with metformin during pregnancy. The absence of precise psychiatric diagnoses provided by participants constitutes a limitation, as it may serve as a confounding factor, exerting an influence on maternal health during the perinatal period. It is important to highlight that a history of depression, a well-documented risk factor, could impact the development of depression during this phase (Morrison et al., 2016). Although psychotropic drugs are associated with weight gain and metabolic complications including type 2 diabetes, hypertension, and dyslipidemia (Bhuvaneswar et al., 2009), this is still controversial in a GDM population (Lopez-Yarto et al., 2012). Importantly, the administration of psychotropic drugs during the perinatal period was not systematically documented in medical charts but is rare in our current practice in pregnancy. Furthermore, we focused on “women” and not “mothers” to avoid too much complexity, but we do, of course, consider this time in life as a critical period. The influence of GDM may significantly impact on their anxiety regarding neonatal birth outcomes and these outcomes may also influence maternal mental health. We do not, however, include outcomes for the infant in this study, as our aim was to focus on the complex trajectories and intraindividual variability of different mental health, well-being, and metabolic health outcomes in women with GDM, but this has been previously done (Gilbert et al., 2023).

4.2. Implications for practice and research

Findings from this study reinforce the need to integrate mental health screening in GDM care both during pregnancy and in the postpartum also in view that it might be more modulable. According to the multiple pathways identified for symptoms of depression across perinatal period, individualized approaches for the care of mental health and well-being among GDM women are needed. The impact of screening and treatment of symptoms of depression and anxiety on further mental and metabolic health in pregnancy should be evaluated, particularly in metabolically high-risk patients. We can also observe, that in the context of a regular clinical follow-up, depression symptom scores, even in a high-risk population, are relatively low. Acquiring more knowledge about mental health during the perinatal period and how it is linked to insulin resistance would provide clinical keys to manage these two conditions.

5. Conclusion

While insulin resistance fluctuates with values being lowest in the early postpartum, mental health improves between pregnancy and the postpartum periods in women with GDM in the context of a clinical follow-up. Despite a higher prevalence of depression symptoms in women with GDM, we found only few significant associations between mental health and metabolic health outcomes. Intraindividual variability over time was higher for mental health than for metabolic health outcomes. There is the need to screen women with GDM for symptoms of depression especially during pregnancy and should continue up to 1-year postpartum to offer mental health support to women.

CRediT authorship contribution statement

Ludmila Nicolazzi: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Supervision; Validation; Visualization; Roles/Writing - original draft; and Writing - review & editing. **Leah Gilbert:** Data curation; Methodology; Roles/Writing - original draft; and Writing - review & editing. **Antje Horsch**: Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Roles/Writing - original draft; and Writing - review & editing. **Dan Yedu Quansah**: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Software; Supervision; Roles/Writing - original draft; and Writing - review & editing. **Jardena J Puder**: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Roles/Writing - original draft; and Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2023.106919.

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